III. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 1 and 3-24 are currently pending and remain at issue in this application. This response is timely filed as it is accompanied by a petition for an extension of time to file in the third month and the requisite fee.

Amended claim 1 is directed to a method for therapeutic management of infertility and increasing the quality of fertilized oocytes and embryos by programming controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) in order to optimize oocyte harvesting and fertilization, the method comprising the following steps (a) programming the start of controlled ovarian stimulation by resetting the menstrual cycle through administration of a compound selected from the group consisting of a LHRH antagonists, a progestogen only preparation, a combined oral contraceptive preparation, and a combination thereof wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abavelix and is administered at a dosage range between 0.5 mg to 10 mg during the luteal phase of the menstrual cycle to induce luteolysis, and wherein the progestogen only preparations and/or the combined oral contraception preparations are administered starting during both the luteal phase and day 1 or 2 of the menstrual cycle; (b) exogenous stimulation of the ovarian follicle growth via administration of a compound selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, and a combination thereof; (c) suppression of premature ovulation via administration of a LHRH-antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abavelix during the follicular stage of the menstrual cycle; (d) induce ovulation via administration of HCG; and (e) application of assisted reproduction techniques, especially IVF, ICSI, GIFT, ZIFT or by intrauterine insemination via sperm injection. Support for amended claim 1 can be found throughout the specification, for example, on page 2, line 24-26; page 2, line 29 to page 4, line 6; and originally filed claim 3.

Additional Fees

Although the applicants believe additional fees (beyond those presented herein) are not necessary for entry and consideration of this amendment/response and entry of the RCE,

should the USPTO determine additional fees are due (for such consideration), the Patent Office is authorized to charge such fees to USPTO Deposit Account No. 03-3975.

The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications. The applicants request entry of the foregoing amendment, as it will either place the application for allowance or place the application in better form for continued examination.

Patentability Remarks

Rejection Pursuant to 35 U.S.C. §103(a), Obviousness

On pages 2-9, the examiner maintained the rejection of claim 1 and 4-24 under 35 U.S.C. §103(a) over Engel *et al.*, EP 0788799 (hereafter Engel), Albano *et al., Human Reproduction* 11:2114-2118 (1996; hereafter Albano), Felberbaum *et al.*, 10th World Congress on *In Vitro Fertilization and Assisted Reproduction* 397-404 (hereafter Felberbaum), and Garfield *et al.*, U.S. Patent No. 5,470,847 (hereafter Garfield) in view of Deghenghi, U.S. Patent No. 5,945,128 (hereafter Deghenghi), Rabasseda *et al.*, *Drugs of the Future* 24:393-403 (1999; hereafter Rabasseda), and Kent, U.S. Patent No. 4,016,259 (hereafter Kent). On page 7 of the official action, the examiner asserted that the primary references Engel, Albano, Felberbaum and Garfield disclose methods for the treatment of infertility disorders and suppression of premature ovulation in controlled ovarian stimulation and assisted reproductive techniques. The examiner further asserted that the instant LHRH-antagonists such as teverelix, antide, and abarelix are known to be LHRH-antagonists and useful in the treatment of infertility according the techniques described in Engel, Albano, Felberbaum, Deghenghi and Rabasseda. The examiner stated the rearranged steps of claim 1 are not critical for employing one of ordinary skill in the art with the treatment and management of administering known active agents. The examiner further asserted that one of ordinary skill in the art would have reasonably expected that combining oral contraceptive preparations in combination with progestogen would produce additive therapeutic effects to improve the treatment and therapeutic management of infertility. In addition, the examiner alleged that the results provide no clear and convincing evidence of non-obviousness or unexpected results over the cited prior art since there is no side by side comparison. Accordingly, the examiner did not deem persuasive the applicants' results of the instant

method in the specification on page 4 and 5 with respect to unexpected results of the claimed invention over the prior art.

The applicants hereby submit a declaration under 37 C.F.R. §132 by Dr. Hilde Riethmuller Winzen, a named co-inventor, attesting to the fact that the claimed method is novel and unobvious over the cited prior art. Specifically, the administration of progesterone only, or progestogen or progestogen plus oral contraceptives in combination with LHRH antagonists during the luteal phase of the menstrual cycle causes luteolysis or a resetting of the menstrual cycle to enable one to program and specifically time COS/ART procedures. In addition, the administration of progestogen/contraceptive preparations and/or an LHRH antagonists during the luteal phase of the menstrual cycle not only provides physicians more flexible scheduling of COS/ART procedures in a fertility center, but also improves and homogenizes the size of the recruited follicles to improve the quality of fertilized oocytes and embryos.

The applicants submit that none of the references discussed above would fail to motivate one of skill to optimize the treatment of female infertility by programming the controlled ovarian stimulation protocol and assisted reproductive techniques. This programming is dependent upon the novel discovery that administration of oral contraceptives in the form of progestogens or progestogens with estrodiol can be used to reset the menstrual cycle. In addition, the further administration of LHRH antagonists such as cetrorelix can be used to induce luteolysis during the luteal phase of the menstrual cycle and program the onset of a new menstrual cycle . The timing of these procedures allows for the stimulation of oocytes from a Friday to a Monday, an oocyte pick up and fertilization by ART protocols between Monday and Friday. This predictable, manipulable program which manages overcoming infertility in a woman, is neither taught nor disclosed by the seven publications discussed above.

The applicants, by use of Dr. Riethmüller-Winzen's declaration, have performed a side-by-side comparison of each cited references concluding that none of the references individual or in combination teach the application of progesterone only, or progestogen or progestogen plus oral contraceptives in combination with LHRH antagonists starting during the luteal phase or 1 or 2 days of the follicular phase for resetting the menstrual cycle and programming the exact day of ovarian stimulation and assisted reproductive techniques. In fact, the combined teaching of the references cited in the official action state that combining

progesterone and LHRH antagonists during any stage of the menstrual cycle would have deleterious effects on growing follicles and oocytes using COS protocols, and thus inhibiting successful implantation of good quality embryos using ART protocols.

Contrary to these teachings, the applicants have described that LHRH antagonist can be used effectively in two stages of the menstrual cycle. LHRH antagonists can be used during the luteal phase to induce luteolysis and reset the menstrual cycle. LHRH antagonist can also be used during the follicular phase either for a few days (if using multiple dose regimen), or one or two days (if using a single dose regimen) before ovulation induction by HCG. Accordingly, in view of the foregoing declaration, the applicants respectfully submit that the claimed invention is not obvious in view of the cited art in the current obviousness rejection.

In her declaration, Dr. Riethmüller-Winzen further describes two clinical studies that verify and discuss the secondary benefits of the claimed method (*see* Fanchin *et al., Reprod. Biomed. Online* 10:721-728 (2005) and Hugues, "Medical, Ethical, and Social Aspects of Assisted Reproduction" held at WHO Headquarters in Geneva, Switzerland). Specifically, one secondary benefits of the claimed method is the homogenization of the antral follicle sizes that are often markedly heterogenous during the early follicular state.

In view of the foregoing, the applicants submit that the claimed method is unobvious over the disclosed methods of Engel, Albano, Felberbaum, and Garfield in view of Deghenghi, Rabasseda, and Kent either alone or in combination. In view of the foregoing amendment and remarks, the applicants respectfully request that the rejection of claims 1 and 4-24 under 35 U.S.C. §103(a) as allegedly being obvious over Engel, Albano, Felberbaum, and Garfield in view of Deghenghi, Rabasseda, and Kent, has been overcome and should be withdrawn.

Rejection Pursuant to the Judicially Created Doctrine of Obviousness Double Patenting

On pages 9 and 10 of the official action, the examiner rejected claims 1 and 3-24 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,319,192. Specifically, the examiner asserted that although the conflicting claims were not identical, they were not patentably distinct from each other because the patent is drawn to a method of therapeutic management of infertility by intrauterine insemination consisting of substantially similar method steps and administering the same pharmaceutical agents (LHRH-antagonists such as cetrorelix, HCG,

native LHRH, LHRH-agonists, or recombinant LH). The examiner asserted that the claim limitation of COS/ART procedures is obvious in view of U.S. Patent No. 6,319,192 since COS/ART procedures were well known in the art. The examiner concluded, the major steps claimed are thus disclosed in the patent.

As stated in the previous response, the applicants resubmit that the novel step of resetting the menstrual cycle using progesterone only, or progestogen or progestogen plus oral contraceptives in combination with LHRH antagonists during the luteal phase and early stages of the follicular stage to reset the menstrual cycle is patentably distinct over the claimed methods of the '192 patent. Nowhere in the disclosure of the '192 patent or the claimed invention is there a teaching or suggestion regarding the importance of programming the COS/ART procedures by resetting the menstrual cycle using progestogen or other oral conceptive preparations. This novel finding allows physicians to optimize the controlled stimulation of the ovaries and fertilize the eggs using assisted reproductive techniques. As discussed above, claim 3 has been canceled without prejudice. Nevertheless, to expedite prosecution, the applicants will consider filing a terminal disclaimer, if the rejection is maintained when one or more claims in the instant application are in a condition for allowance. In view of the foregoing remarks, the applicants have noted the provisional rejection by the examiner.

CONCLUSION

In view of the foregoing, the claims are now believed to be in form of allowance, and such action is hereby solicited. If any point remains at issue which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number below.

Respectfully submitted,

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